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Appendectomy in Adulthood and the Risk of Inflammatory Bowel Diseases

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Background: There is controversy as to whether appendectomy protects against the development of ulcerative colitis, but the possible impact of appendectomies performed in adulthood has not been systematically investigated. **Methods:** We conducted a large case-control study based on inpatient records from Veterans Affairs hospitals in the United States for the period 1969–96. We identified 6,172 male patients with ulcerative colitis (age range 19–101 years, mean 57.4 years) and 4,498 male patients with Crohn disease (age range 18–99 years, mean 52.9 years). Each of these case patients was individually age- and race-matched to five other male veterans without recorded history of inflammatory bowel disease. We compared records of prior appendectomies in adulthood for the matched case-control sets using conditional logistic regression. **Results:** Overall, both ulcerative colitis (odds ratio (OR) = 1.6, 95% confidence interval (CI): 1.3–2.1) and Crohn disease (OR = 2.5, 95% CI: 2.0–3.3) were significantly and positively associated with history of appendectomy in adulthood. However, risks were not increased at intervals of 15 years or more between appendectomy and inflammatory bowel disease (ulcerative colitis: OR = 0.9, 95% CI: 0.4–2.1; Crohn disease: OR = 1.2, 95% CI: 0.5–2.5). **Conclusions:** The elevated risk of inflammatory bowel disease, notably Crohn disease, after appendectomy probably reflects differential diagnostic difficulties in patients with abdominal pain. Appendectomy carried out during adulthood seems not to confer protection against ulcerative colitis.

Key words: Appendectomy; Crohn disease; ulcerative colitis

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A large number of case-control studies (1–15) have led to the widely held belief that appendectomy is inversely related to the risk of ulcerative colitis. This impression has been stimulated by the observation that appendectomy exerts a protective effect against colonic inflammation resembling ulcerative colitis in T-cell receptor-alpha mutant mice (16). However, extrapolation from findings in genetically engineered mice to the human setting is problematic, and there is currently no convincing biologic explanation of an inverse association in man. Recently, we have discussed the multitude of methodological problems (17, 18) that have hampered most prior studies (1–15), and we have provided evidence from a cohort of 154,434 appendectomized patients to suggest that appendectomy and its underlying causes are not biologically related to the risk of ulcerative colitis (17). Since appendectomies in prior studies were dominated by operations performed during childhood or adolescence, we found it of interest to investigate these issues further in a large study of the impact of appendectomies performed in adulthood. Consequently, we compared histories of appendectomy performed at or after the age of 21 years in a large group of subjects with ulcerative colitis or Crohn disease and a group of control subjects without either of these inflammatory bowel diseases.

Methods

We conducted a matched case-control study using computerized records for inpatients treated at Veterans Affairs (VA) hospitals across the United States, as described elsewhere (19). The following International Classification of Diseases (ICD) discharge codes were used to identify subjects with ulcerative colitis (ICD-8 = 563.1 or ICD-9 = 556) or Crohn disease (ICD-8 = 563.0 or ICD-9 = 555), who were hospitalized between 1 July 1969 and 30 September 1996. After excluding patients whose first VA hospitalization was for ulcerative colitis or Crohn disease and those who had appendectomy at their first VA hospitalization for inflammatory bowel disease (i.e. subjects who did not contribute information on the putative modifying role of prior appen-

Table I. Odds ratio (OR) and 95% confidence interval (CI) for history of appendectomy in adulthood among patients with ulcerative colitis and Crohn disease. Veterans Affairs case-control study, 1969–96

	Ulcerative colitis			Crohn disease		
	Cases/controls*	OR	(95% CI)	Cases/controls*	OR	(95% CI)
Appendectomy						
No	6,098/30,632	1	(referent)	4,400/22,294	1	(referent)
Yes	74/228	1.6	(1.3–2.1)	98/194	2.5	(2.0–3.3)
Age at appendectomy						
21–34 years	8/29	1.4	(0.6–3.0)	34/30	5.7	(3.5–9.6)
35–44 years	4/32	0.6	(0.2–1.8)	17/32	2.7	(1.5–4.9)
45–54 years	10/34	1.5	(0.7–3.0)	18/38	2.4	(1.4–4.3)
55+ years	52/133	2.0	(1.4–2.7)	29/94	1.5	(1.0–2.4)
Time since appendectomy						
1 year	14/36	1.9	(1.0–3.6)	32/16	10.0	(5.5–18.3)
2–4 years	16/61	1.3	(0.8–2.3)	33/52	3.2	(2.1–4.9)
5–14 years	38/97	2.0	(1.4–2.9)	25/92	1.4	(0.9–2.1)
15+ years	6/34	0.9	(0.4–2.1)	8/34	1.2	(0.5–2.5)

* Cases were 6,172 male veterans with ulcerative colitis and 4,498 with Crohn disease. Individually age- and race-matched controls (five controls per case, except two cases who had only four controls) were male veterans with no recorded history of inflammatory bowel disease.

dectomies), our case groups comprised 6,172 male veterans (90% whites, 10% blacks) with ulcerative colitis and 4,498 male veterans (88% whites, 12% blacks) with Crohn disease.

For each case we identified five individually matched male control subjects in the VA files who had no records of inflammatory bowel disease. For two men with Crohn disease, however, only four controls were identified. Control subjects were matched on race, year of birth and year of first hospitalization in a VA hospital, and they had to be alive on the date of the first hospitalization for inflammatory bowel disease in the corresponding case. This matching procedure ensured that cases and controls had identical ascertainment periods for prior appendectomies, a basic requirement for unbiased analysis which was not met in several prior case-control studies (4–7, 12). Numbers of case and control subjects with a record of appendectomy in adulthood (ICD-8 operation codes 41.0–41.9 or ICD-9 operation codes 47.0–47.9) prior to the date of first recorded hospitalization for inflammatory bowel disease in the case were compared using conditional logistic regression (20). Odds ratios (ORs) with 95% confidence intervals (CIs) served as estimates of the relative risk.

Results

Mean ages at first VA hospitalization for ulcerative colitis and Crohn disease were 57.4 years (range 19–101 years) and 52.9 years (range 18–99 years), respectively. Mean ages at first VA hospitalization for any reason were 49.9 years (range 17–95 years) for patients with ulcerative colitis and their respective controls and 45.7 years (range 17–94 years) for patients with Crohn disease and their respective controls. Accordingly, the time interval for ascertainment of prior appendectomies (i.e. the time interval between first VA hospitalization for any reason and the first VA hospitalization for inflammatory bowel disease in the case) ranged from less than 1 month to 27.3 years (mean 7.5 years for ulcerative colitis and 7.2 years for Crohn disease).

Overall, patients with inflammatory bowel diseases were significantly more likely to have been appendectomized in adulthood than their individually matched controls (ulcerative colitis; OR = 1.6, 95% CI: 1.3–2.1, Crohn disease; OR = 2.5, 95% CI: 2.0–3.3) (Table I). While age at appendectomy was not systematically associated with risk of ulcerative colitis, the highest risk of Crohn disease was seen among patients appendectomized before age 35 years (OR = 5.7, 95% CI: 3.5–9.6). When analyzed according to interval between appendectomy and inflammatory bowel disease, odds ratios associated with appendectomy were above unity up to 15 years before the time of inflammatory bowel disease in the cases. However, no significant association was present for intervals of 15 years or longer (ulcerative colitis; OR = 0.9, 95% CI: 0.4–2.1, Crohn disease; OR = 1.2, 95% CI: 0.5–2.5).

Discussion

This study, the largest case-control study evaluating the role of appendectomy in inflammatory bowel disease to date, suggests that appendectomy in adulthood is not inversely associated with ulcerative colitis risk. The significantly elevated risk of both major types of inflammatory bowel disease shortly after appendectomy, notably Crohn disease, most likely reflects differential diagnostic problems in patients presenting for the first time with abdominal pain.

Our study has limitations. The male gender and age composition of the patients studied precludes an evaluation of the impact of appendectomy among women and during childhood on the risk of ulcerative colitis. Also, despite our ability to evaluate the role of prior appendectomy up to 27 years before first hospitalization for ulcerative colitis or Crohn disease, the mean time interval between the first VA

hospitalization for any reason and ulcerative colitis—the average period during which recorded appendectomies could have occurred—was only 7.5 years. Also, some patients with inflammatory bowel disease treated at VA hospitals may have had appendectomies performed elsewhere. To the extent such missed appendectomies occurred selectively in control subjects, our odds ratios may be too high. However, similar risk patterns were seen for both ulcerative colitis and Crohn disease with elevated odds ratios associated with appendectomy shortly before the inflammatory bowel disease and no significant association with appendectomy performed more than 15 years before. Since no previous study has suggested that appendectomy protects against the development of Crohn disease, it is unlikely that the lack of an inverse association between appendectomy and risk of either of the two inflammatory bowel diseases would be the result of design-related limitations.

In a recent population-based cohort study in Denmark, we observed no statistically significant association between appendectomy and ulcerative colitis risk among 154,434 patients appendectomized at median ages of 21 years (men) and 28 years (women) who were followed for inflammatory bowel diseases during more than one million person-years (17). In combination with the present study, our findings suggest that appendectomy, whether performed during childhood, adolescence or adulthood, does not impact biologically on the subsequent risk of ulcerative colitis or Crohn disease.

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